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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/731,550	12/09/2003	Ole Isacson	083883-0302	4567

30542 7590 07/12/2007
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

MAIL DATE	DELIVERY MODE
07/12/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/731,550	ISACSON ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8 and 15-20* is/are pending in the application.

4a) Of the above claim(s) *2,7 and 17-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,15 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4-27-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office action is in response to the communication filed 4-27-07.

Claims 1-8 and 15-20 are pending in the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

This application contains claims 2, 7 and 17-20 drawn to an invention nonelected with traverse in the election filed 10-31-06. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Response to Arguments and Amendments

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

Maintained Rejections

Claims 1, 3-6, 8, 15 and 16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating gene expression profiles of in vitro differentiation of previously generated Smad4 -/- and Cripto -/- mouse embryonic stem cells (ESC) using a five-stage differentiation protocol, and for transplantation of Smad4 -/- and Cripto -/- grafts in mice in vivo, whereby expression of

neuron associated genes in these grafts were not statistically significant compared to WT grafts, does not reasonably provide enablement for methods for generating dopaminergic neurons in vitro or in vivo comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent cells for the reasons of record set forth in the Office action mailed 1-31-07.

Applicant's arguments filed 4-27-07 have been fully considered but they are not persuasive. Applicants argue that the instant claims are enabled for the full scope claimed because the specification provides a working example of the inhibition of Smad4 in pluripotent cells and characterizes certain properties of those cells. Applicant also argues that the specification provides direction for multiple methods of Smad4 inhibition that fully enable the in vitro inhibition of Smad 4.

Contrary to Applicant's assertions, the instant claims are not enabled. Applicants have not provided sufficient guidance in the specification toward a method of generating dopaminergic neurons in vitro in ES cells (including human) comprising inhibiting any pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing any cell fate-inducing polypeptides in the target pluripotent cells. The instant disclosure teaches gene expression profiles of in vitro differentiation of previously generated Smad4 -/- and Cripto -/- mouse embryonic stem cells (ESC) using a five stage differentiation protocol, as well as the increased expression of mesencephalic dopaminergic markers (e.g. Nurr-1) during later stages of in vitro differentiation of Smad4 -/- and Cripto -/- ES cells. The specification also teaches the

general availability from previous investigators of cell lines which overexpress some cell fate inducing genes. The specification teaches the transplantation of Smad4 -/- and Cripto -/- grafts in mice in vivo, whereby expression of neuron associated genes in these grafts was not statistically significant compared to wild type grafts

These teachings are not representative or correlative of the ability to generate dopaminergic neurons in vitro comprising inhibiting one or more pathway components of a TGF-β signaling pathway in any pluripotent target cells and overexpressing one or more cell fate-inducing polypeptides in the target pluripotent cells. The correlation of phenotypes in previously generated Smad4 -/- and Cripto -/- cells is not representative of the ability to inhibit the appropriate target genes in cells (e.g. using antisense or other methods of inhibition) whereby the level of appropriate target gene inhibition is achieved in those cells and dopaminergic neurons are generated in vitro. The protocol provided in the instant specification is not representative or correlative of overcoming the delivery obstacles that target gene inhibition present using antisense or other inhibitory molecules.

The specification as filed fails to provide any particular guidance which resolves the known unpredictability in the art associated with delivery and the subsequent inhibition of any TGF-β signaling pathway component or overexpression of any cell fate inducing gene, whereby dopaminergic neurons are generated in vitro or in vivo. The specification as filed fails to provide the specific guidance necessary for the skilled artisan to carry out the entire protocol with any predictable degree of success. The quantity of experimentation required to practice the invention as claimed would require

the *de novo* determination of accessible target sites, modes of delivery and formulations to target appropriate cells and /or tissues whereby dopaminergic neurons are generated in vitro following administration of inhibitory agents to the pluripotent target cells whereby altered expression of the requisite target genes is achieved, and which are appropriately inhibited or overexpressed. Since the specification fails to provide sufficient guidance for the generation of dopaminergic neurons using any of the methods claimed, it would require undue experimentation to practice the invention over the broad scope claimed. For these reasons, the instant rejection is maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices

published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. ' 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jane Zara whose telephone number is (571) 272-0765. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Douglas Schultz, can be reached on (571) 272-0763. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jane Zara
7-6-07

JANE ZARA, PH.D.
PRIMARY EXAMINER